

7. Please provide more detailed formulation information.
8. Please refer to the ICH Stability Guidelines for study conditions.

ACTION ITEMS: None

The meeting was concluded at 1:40 pm. There were no unresolved issues or discussion points.

/S/

Patrick Guinn, Project Manager
Minutes preparer


Concurrence Chair: _____


/S/

Chengyi Liang, Ph.D.
Chemistry Reviewer

/S/

7/24/98

IND - 
Meeting Minutes
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cc:
Original IND - 
HFD-150/Div File
/PGuinn

cc electronically only:

Choiberg
JSimmons
LZhou
CLiang
XChen
NChidambaram
PGuinn
DPease
LVaccari

MEETING MINUTES

MEETING MINUTES

MEETING DATE: July 23, 1998 TIME: 10:00 am LOCATION: Conf. Rm. G

IND Meeting Request Submission Date: May 18, 1998
Briefing Document Submission Date: June 22, 1998

DRUG: Epirubicin Hydrochloride

SPONSOR/APPLICANT: Pharmacia & Upjohn

TYPE of MEETING:

1. Pre-NDA
2. Proposed Indication: Adjuvant treatment of patients with node-positive early breast cancer and for the treatment of patients with advanced/recurrent breast cancer

FDA PARTICIPANTS:

Dr. Beitz	- Acting Deputy Director
Dr. Williams	- Medical Team Leader
Dr. Honig	- Medical Officer
Dr. Zhou	- Chemistry Team Leader (pre-meeting only)
Dr. G.Chen	- Biometrics Team Leader
Dr. Rahman	- Biopharmaceutics Team Leader (pre-meeting only)
Dr. Ibrahim	- Biopharmaceutics Reviewer
Mr. P.Guinn	- Project Manager

INDUSTRY PARTICIPANTS:

Mark Griso- Director, Global Regulatory Affairs (Italy)
Langdon Miller, M.D. - Clinical Development (US)
Claudio Praga, M.D. - Pharmacovigilance (Italy)
Anna Petroccione - Biostatistics (Italy)
Marcello Riggi, M.D. - Clinical Development (Italy)
Denise Tindle - Regulatory Affairs Manager (US)
Alberto Fittapaldo - Project Manager
Italo Pogessi - Pharmacokinetics

MEETING OBJECTIVES:

To discuss the plans for a submission of an NDA for epirubicin hydrochloride for the treatment of breast cancer.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. The basic pharmacokinetics of epirubicin for injection will be supported in the NDA by the data from the internal report by Camaggi. The information relating to factors that affect epirubicin pharmacokinetics and pharmacokinetic/pharmacodynamics relationships will be supported in the NDA by selected original published papers as described in this background document. Is this approach considered adequate for an NDA?
 - Yes, but only relevant peer reviewed articles that address the claims made in the package insert for epirubicin should be submitted.
2. P&U intends to presubmit Items 5 and 6 to IND — Is this acceptable to FDA?
 - Yes. However, both Items 5 and 6 should be submitted in the NDA as well.
3. As outlined in Tables 4 and 6 of this background document, P&U intends to include in the NDA study reports, case report tabulations (CRTs), case report forms (deaths, drop-outs due to adverse events, secondary leukemias, and cardiotoxicity) for the pivotal studies in early (MA-5) and advanced (HEPI013) breast cancer. Study reports and CRTs will be submitted for the supportive studies that used combination epirubicin therapy (GFEA05 in early breast cancer and HEPI010 in advanced breast cancer). Only study reports will be provided for the other supportive studies, i.e., single-agent epirubicin studies in each indication (C/4/87 in early breast cancer and — in advanced breast cancer). Does the FDA agree with this approach?
 - Independent verification of study results is required for each indication, with FDA review of both studies. CRFs should therefore also be submitted for the supportive studies designated for each indication.
 - For the other supportive studies, P&U's approach is acceptable.

⇒ A copy of the CRF forms translated from French will be provided as an example, in order to agree upon an appropriate format.

⇒ A proposal for timing of submission of translated CRFs will be provided by Pharmacia & Upjohn. (possibly submit translated CRFs after filing of the NDA)
4. P&U proposes to provide summaries of only those published articles that provide information relevant to an assessment of the efficacy and safety of epirubicin for the treatment of breast cancer and will select these articles according to predefined criteria, as

summarized in this background document. Tabular summaries of data will be prepared for these relevant articles; articles will be grouped by study design (as summarized in the background document) and a narrative summary will be prepared to review the findings across studies. A bibliography of all articles (including the excluded articles) that have been published on the use of epirubicin in breast cancer (from the publication of the first article through June 1998) will be provided in the NDA. Only copies of the articles for which summaries are prepared will be provided in the NDA. Does FDA agree with this approach, the proposed selection criteria, and the proposed organization of the published data?

- Yes, this plan, the selection criteria, and the data organization are acceptable. Where available, please provide confidence intervals and p-values for results.
- Please note, however, that for the indication for first-line treatment of metastatic breast cancer, you must include trials of doxorubicin-based therapy compared to epirubicin-based therapy as first-line therapy of MBC. Detailed discussions and summaries of these studies are necessary to demonstrate that epirubicin is unlikely to be worse than doxorubicin in order to obtain approval.

⇒ Reference for statistical approach will be provided by FDA. (2 papers)

⇒ A proposal for selection criteria of relevant papers for epirubicin/doxorubicin comparison will be provided by Pharmacia & Upjohn. However, an overview of all comparisons of epirubicin/doxorubicin should be included.

5. Due to the differences in study designs among the studies in early breast cancer and among those in advanced breast cancer (as outlined in the background document), P&U does not intend to integrate either efficacy or safety data across the early breast cancer studies or across the advanced breast cancer studies. Does FDA agree with this approach?
 - No, we do not. While we recognize that the differences in study design will not permit the usual detailed ISE and ISS, you should provide an integrated overview of safety for both early and metastatic breast cancer that directly supports your labeling claim. (we suggest lumping FEC 100 and FEC 120 safety information for each indication)
6. Efficacy and safety data for each individual study will be summarized using the tabular formats for early breast cancer and advanced breast cancer studies, as provided in the background document. Are these data displays acceptable to FDA?

- Yes, they appear to be acceptable at this time.
 - Please provide a detailed definition of febrile neutropenia for each study.
7. As mentioned in our correspondence dated June 16, 1998, in order to provide a post-marketing safety profile for epirubicin, P&U intends to include a Safety Report in the NDA which will cover the period from July 1, 1993 to June 30, 1998 and which will be prepared according to the ICH-E2C guideline. In addition, a safety review, which is mainly focused on cardiotoxicity and which was prepared in 1990 based on data from 9144 patients, and data listings, with comments, of all serious and non-serious unexpected adverse reactions entered in the Company data base between January 1, 1990 and June 30, 1993 will be included. The above mentioned pharmacovigilance data will represent the reference documentation for the ISS since the first marketing date worldwide. Is this approach acceptable to FDA?
- Yes, it is.
8. P&U intends to submit Items 11 (CRTs) and 12 (CRFs) electronically. Is this acceptable to FDA?
- Yes, it is.

Additional comments from DODP from review of the background document: (page numbers coincide with the numbers listed at the bottom of the pages in the meeting package)

1. Why won't trial BE85008 (Focan et al) be included as a supporting trial for first-line treatment of metastatic breast cancer? This study, in contrast to HEPI010, showed a statistically significant benefit for high-dose FEC in time to progression compared to "low-dose" FEC. Did P&U make this choice based on the number of patients enrolled (164 compared to 456 in HEPI010)? Why not submit both as supporting studies?
 - ⇒ We would prefer to have the study report and protocol, not just the publication. (CRFs and CRTs will not be necessary). Pharmacia & Upjohn will include trial BE85008 as an "additional supportive study".
2. On page 20 of the briefing document, patients in the early stage breast cancer trials will be analyzed according to the treatment actually received. The DODP considers the intent-to-treat analysis, where patients are analyzed according to randomized treatment, as the primary analysis.

3. On page 20 of the briefing document, P&U states that only randomized patients who received at least one cycle of therapy and who have at least one on-therapy assessment will be included in the safety analysis. All patients who received study drug should be included in the safety assessment.
4. On page 21, please add primary tumor size (whatever is available, pathology/clinical) to the baseline patient characteristics that will be described. Is there flow cytometry data available for these patients?

⇒ Pharmacia & Upjohn states that if it was done, it was in an exploratory manner. They will include these data if available.

5. On page 23, for early stage breast cancer, the sponsor states that quality of life data will be analyzed for all forms which have complete answers to all questions. This approach will potentially exclude many patients and/or time points in a non-random fashion, as decreased quality of life or toxicity may have caused patients to only complete part of the form. You should evaluate all forms and discuss procedures for handling non-random missing data with the FDA statistical reviewers.

⇒ References will be provided by FDA.

6. On page 25, the sponsor plans to list all patients who experienced a drop in LVEF below the normal range. Please also include all patients who experienced an absolute decrease in the LVEF by $\geq 20\%$ from baseline and all patients who experienced any cardiac toxicity that required a treatment interruption.

⇒ This can be done.

7. On page 26, the sponsor states that standard WHO criteria for response were used. Does this mean that confirmation of response at 3 or 4 weeks was required?

⇒ Yes.

Please define these criteria in each study report.

8. On page 27, the sponsor plans to include patients who have received at least 2 cycles of chemotherapy in the efficacy analysis, unless there has been rapid disease progression or death. The DODP considers the intent-to-treat analysis, where patients are analyzed according to randomized treatment, as the primary analysis.

⇒ This is intended to be an additional analysis and applies to evaluable patient analysis.

9. Re: Table 3 (page 14)

The protocol-specified analysis (logrank test) should be provided.

⇒ This Table is based on logrank test.

10. Please refer to our handouts regarding electronic data submission.

- Statistical: Datasets should be submitted in SAS 6.11 or higher for Windows 95.
- Medical: Datasets should also be submitted in Access for Windows 95.
- Specific electronic format was provided in a Handout at the meeting. (4 pages)

ACTION ITEMS:

1. A copy of the CRF forms translated from French will be provided by Pharmacia & Upjohn as an example, in order to agree upon an appropriate format.
2. A proposal for timing of submission of translated CRFs will be provided by Pharmacia & Upjohn. (possibly submit translated CRFs after filing of the NDA)
3. Reference for statistical approach will be provided by FDA. (2 papers)
4. A proposal for selection criteria of relevant papers for epirubicin/doxorubicin comparison will be provided by Pharmacia & Upjohn. However, an overview of all comparisons of epirubicin/doxorubicin should be included.
5. You should evaluate all forms and discuss procedures for handling non-random missing data with the FDA statistical reviewers. References will be provided by FDA.

The meeting was concluded at 11:20 am. There were no unresolved issues or discussion points.

~~/S/~~ 7/23/98
Patrick Guinn, Project Manager
Minutes preparer

Concurrence Chair:

~~/S/~~ 7/23/98
Susan Honig, M.D.
Medical Officer

IND —
Meeting Minutes
Page 7

cc:
Original IND —
HFD-150/Div File
/PGuinn

cc electronically only:

RTemple
RBehrman
RJustice
JBeitz
GWilliams
SHonig
LZhou
CLiang
PAndrews
DYLeeham
GChen
ARahman
SIbrahim
PGuinn
DPease
LVaccari

MEETING MINUTES

MEETING MINUTES

MEETING DATE: April 9, 1998 TIME: 2:00 p.m. LOCATION: Conference room E

IND Meeting Request Submission Date: January 21, 1998
Briefing Document Submission Date: March 9, 1998

DRUG: Pharmorubicin PFS (Epirubicin hydrochloride)

SPONSOR/APPLICANT: Pharmacia & Upjohn

TYPE of MEETING:

1. Guidance
2. Proposed Indication: Adjuvant treatment of node positive early breast cancer (EBC) therapy of advanced/recurrent breast

<u>FDA Participants</u>	<u>Sponsor Participants</u>
Dr. Temple - Office Director (pre-meeting only)	Dr. Marcello Riggi - Clin. Devel. (Italy)
Dr. Justice - Division Deputy Director	Dr. Alberto Fittipaldo - Clin Devel. (Italy)
Dr. Williams - Medical Team Leader	Dr. Silvia Caglio - Clin. Devel. (Italy)
Dr. Honig - Medical Officer	Dr. Langdon Miller - Clin. Devel. (US)
Dr. Zhou - Chemistry Team Leader	Dr. Mark Griso - Reg. Affairs (Italy)
Dr. Liang - Chemistry Reviewer	Dr. Laura Marmonti - Reg. Affairs (Italy)
Dr. Andrews - Pharmacology Team Leader	Dr. Daniel Mannix - Reg. Affairs (US)
Dr. Lee-Ham - Pharmacology Reviewer	Ms. Karin Weston - Reg. Affairs (US)
Dr. Koutsoukos - Biometrics Team Leader	<u> </u> Consultant
Dr. Takeuchi - Biometrics Reviewer	
Dr. Rahman - Biopharm Team Leader	
Dr. Ibrahim - Biopharm Reviewer (pre-meeting only)	
Mr. P.Guinn - Project Manager	

MEETING OBJECTIVE:

To discuss the adequacy of clinical data, from studies conducted outside the United States, to support the submission of an NDA for the use of epirubicin in the treatment of breast cancer.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. CMF is a regimen that has become a well-established standard in the adjuvant treatment of patients with early breast cancer. Until the results of the MA-5 (Study 1) data became available, no prior regimen, with or without anthracyclines, had shown an improvement in survival over CMF. The results of Study 1 indicate that administration of epirubicin as part of the FEC regimen is associated with a 2.7-year relapse-free survival that is significantly better than the 1.9-year relapse-free survival seen with CMF.
Pharmacia & Upjohn believes that these results are clinically relevant. Does FDA concur with this opinion?
 - Yes, the summaries suggest an NDA may be warranted. One published trial reports significantly improved disease-free and overall survival with a doxorubicin-based regimen compared to CMF in node positive breast cancer patients.
 - Study 2 supports the contribution of epirubicin. This study would be considered as supportive to the NDA for this indication.
2. Pharmacia & Upjohn believes that the MA-5 (Study 1) and GFEA 05 (Study 2) clinical studies, which demonstrate statistically significant differences in relapse-free survival and overall survival in favor of high doses of epirubicin, provide suitable, documented support for an NDA for the use of epirubicin in combination with cyclophosphamide and fluorouracil for the adjuvant treatment of node positive, early breast cancer.
Does FDA agree?
 - Yes. Study 1 reported improved RFS and OS for FEC compared to CMF, a community standard for adjuvant therapy; Study 2 reported a dose-response relationship for epirubicin. However, you should provide the number of patients in each nodal stratum (1-3 and > 4) for Study 1 to ensure that benefit was not seen only in patients with high-risk disease.
 - Second, you should note that Study 4 (epirubicin + tamoxifen versus tamoxifen) may support efficacy in postmenopausal patients based on updated analysis.
3. In the first-line therapy of advanced breast cancer, the FEC regimen, containing epirubicin at 100 mg/m², has shown significantly better response rates than CMF. In addition there are supportive studies and numerous publications which also demonstrate that epirubicin is particularly active at these high doses (and also at low doses) in this indication.
Would the package of data comprising results from Study 5 as a pivotal trial and Studies 6, 7 and 8 as supporting trials support an NDA for the use of epirubicin in the FEC combination as first line treatment of advanced breast cancer?

- We believe the package could support an NDA, with some modifications. For first-line therapy of untreated metastatic breast cancer (MBC), meta-analyses have demonstrated a modest survival advantage for doxorubicin-based regimens. Superiority to CMF in the first-line setting supports the activity of epirubicin, but trials of doxorubicin-based therapy compared to epirubicin-based therapy as first-line therapy of MBC are pertinent.
- Three trials were identified in the literature:
 - ◊ Italian Multicentre Breast Study with Epirubicin, J. Clin. Oncol. 1988 Jun; 6(6): 976-82
 - ◊ French Epirubicin Study Group, J. Clin. Oncol. 1988 Apr; 6(4): 679-88
 - ◊ Perez et al, J. Clin. Oncol. 1991 Dec; 9(12): 2148-52

This package, in combination with the planned submission of the dose-response trials of epirubicin, could support the proposed indication.

- We would be glad to discuss with you the presentation of these additional studies. A table should be provided listing all studies and categorized by:
 - ◊ full study reports with data listings
 - ◊ study reports without data listings
 - ◊ published literature

4. A number of Phase IV/post marketing studies are currently on-going, utilizing epirubicin in various combinations in a number of indications. In addition over 2800 publications already exist on epirubicin. If filing for breast cancer is considered possible, the Company deems it unfeasible to submit all data available on epirubicin, as would be required by full disclosure, for the evaluation of safety and proposes to submit a pharmacovigilance report (CIOMS format) updated to 1997.

Is this considered acceptable to FDA?

- A pharmacovigilance report will be submitted to the FDA as an example.
- The FDA will provide any relevant comments concerning the Report and CIOMS format.

5. In the preclinical evaluation of epirubicin most of the toxicological studies were carried out in the late 1970s and early 1980s according to the international regulations in force at that time.

In view of the wealth of published clinical data over the past 15 years, can these studies be considered acceptable today for an epirubicin NDA?

- Yes, this is acceptable from the Pharmacology standpoint

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

1. Information submitted in the Clinical Pharmacology section of the package insert for Epirubicin For Injection should be supported by study data reports that were generated by the sponsor or by adequately validated published data.
2. Information supporting the clinical pharmacology section of the package insert for Epirubicin For Injection should address the following issues: metabolism, mass balance, basic pharmacokinetics, multiple-dose kinetics, dose-proportionality, effect of demographics on drug kinetics (e.g. age, gender, ethnicity, weight, body surface area), effect of disease states on drug kinetics (e.g. hepatic, renal), effect/concentration relationships, potential for drug-drug interactions (e.g. 5-fluorouracil, cyclophosphamide, methotrexate, taxanes), in vitro enzymatic inhibition/induction studies, and in vitro protein binding data.
3. This would likely be considered a priority review.

ACTION ITEM:

You should reactivate IND and submit all information prior to your NDA submission to this IND.

The meeting was concluded at 3:05 p.m..

 4/9/98
Patrick Guinn, Project Manager
Minutes preparer

Concurrence Chair:
Susan Honig, M.D. u
Medical Officer

Attachments: Development Plan
Protocol Summaries

cc:
Original IND/NDA
HFD-150/Div File

/RDeLap
/RJustice
/GWilliams
/SHonig
/LZhou
/CLiang
/PAndrews
/DLeeHam
/TKoutsoukos
/MTakeuchi
/ARahman
/SIbrahim
/PGuinn
/DPease
/LVaccari

HFD-101/RTemple

MEETING MINUTES

EPIRUBICIN HYDROCHLORIDE

APPENDIX 1

Overall development plan

Overall Development Plan 1

Indication:

Early breast cancer

Proposed pivotal trial(s):

Study 1 Code MA-5 (NCIC Group); Principal Investigator: M. Levine

Study 2 Code GFEA 05; Principal Investigator: J. Bonneterre

Proposed supportive trial(s):

Study 3 Code C/2/84 (ICCG); Principal Investigator: R. C. Coombs

Study 4 Code C/4/87 (ICCG); Principal Investigator: J. Wils

Overall Development Plan 2

Indication:

Advanced breast cancer

Proposed pivotal trial(s):

Study 5 Code HEPI 013; Principal Investigator: E. Colajori

Proposed supportive trial(s):

Study 6 Code HEPI 010; Principal Investigator E. Colajori

Study 7 Code BE 85008; Principal Investigator: C. Focan

Study 8

↑
Should I
take out the
whole thing
if this
trial was
not reviewed?
I think I would
It's possible
to research

APPENDIX 2

Protocol Outlines (Pivotal studies)

Protocol Outline

Protocol number/title: MA-5 (NCIC GROUP) / Study on Early Breast Cancer

Objective(s):

(1) to compare the duration of relapse-free survival (RFS) and overall survival (OS) of CEF vs standard CMF

regimen; (2) to estimate the rates of toxicities and to compare the quality of life.

Design: Canadian study, multicenter, open label, randomised phase III trial.

Patient Population:

premenopausal or perimenopausal patients with operable axillary node positive breast cancer, who had undergone complete resection of all known disease by means of total or partial mastectomy.

Dosing plan / treatment plan / schema:

CEF arm: Cyclophosphamide 75 mg/m² orally, d 1 through 14 q.4 weeks
Epirubicin 60 mg/m² I.V., d 1 and d 8 q.4 weeks
5-Fluorouracil 500 mg/m² I.V., d 1 and d 8 q.4 weeks

Patients on the CEF arm received Cotrimoxazole prophylaxis

CMF arm: Cyclophosphamide 100 mg/m² orally, d 1 through 14 q.4 weeks
Methotrexate 40 mg/m² I.V., d 1 and d 8 q.4 weeks
5-Fluorouracil 600 mg/m² I. V., d 1 and d 8 q.4 weeks

Efficacy Endpoints: RFS and OS.

Definition of Endpoints:

RFI: Defined as the time from randomization until the first signs of progressive disease.

OS: Defined as the time from randomization until death from any cause.

Safety Monitoring:

patients on chemotherapy (CT) had a weekly blood test, including platelets and differential WBC; liver function test repeated after 3 and 6 months, and clinical assessment every month. Following CT, assessments were done every 3 months up to 2 years, then every 6 months until 5 years post randomization.

Statistical Plan:

Sample size/basis: sample size was calculated on an improved five year relapse-free survival from 55% with CMF to 65% with CEF, with $\alpha=0.05$, one sided and $\beta=0.20$ (300 patients per treatment arm).

Analyses: The primary response variable was RFS; OS, toxicity rate, and quality of life were the secondary response variables.

Tests on primary and secondary endpoints: RFS of the two treatment groups was described by Kaplan-Meier curves and the stratified Log-Rank Test was the primary method to compare time to an event data of the two treatment groups. The Cox proportional hazards model was used to adjust the observed treatment effect for the influence of various prognostic

factors at study entry. The OS of the groups was described by the Kaplan-Meier method and compared by a stratified Log Rank test. Fisher's Exact test was used to compare the rates of toxicity between treatment arms.

Interim analysis plan: All statistical tests were two-sided. Quality of life was compared by a repeated measures analysis of variance.

Estimated start and completion dates: The study is completed.(1989-1994).

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Protocol number/title: GFEA 05 - Study on Early Breast Cancer.

Objective(s):

Evaluation of two FEC regimens containing either epirubicin 50 mg/m² or epirubicin 100 mg/m² per cycle.

Design:

French study, open label, randomised phase III trial.

Patient Population:

Patients who underwent surgery for breast cancer and showed invasion of axillary lymph nodes and histological grade (SBR) 3.

Dosing plan / treatment plan / schema:

Arm A (FEC 50): 5-Fluorouracil 500 mg/m² iv d 1 q.3 weeks
Epirubicin 50 mg/m² iv d 1 q.3 weeks

Cyclophosphamide 500 mg/m² iv d 1 q.3weeks

Arm B (FEC 100): 5-Fluorouracil 500 mg/m² iv d 1 q.3 weeks
Epirubicin 100 mg/m² iv d 1 q.3 weeks

Cyclophosphamide 500 mg/m² iv d 1 q.3weeks

Tamoxifen (30 mg/d for 3 years, starting on d 1 of the chemotherapy) was added for menopausal patients.

Efficacy Endpoints:

DFS and OS.

Definition of Endpoints:

DFS: Calculated from the date of first surgery to the first date of documented local and/or regional and/or distant failure.

OS: Defined as time in days from the date of surgery to the date of death.

Safety Monitoring:

Patients under chemotherapy were seen every 3 weeks for clinical assessment and hematological assessment.

Statistical Plan:

Sample size/basis: 565/375. The statistical hypothesis is: bilateral test with $\alpha=5\%$ and $\beta=20\%$. The expected improvement of five-years OS is 10% on a basis of 70%.

Analyses: Tolerance and compliance to the treatment, DFS and OS.

Tests on primary and secondary endpoints:

The patients were analyzed in an intent-to-treat analysis.

The comparison of baseline categorical variables and tolerance used a Chi-square test.

The compliance: received/theoretical dose was calculated and RDI is calculated on the basis of 21 days between each cycle

DFS and OS: according to the Kaplan-Meier method.

Interim analysis plan: at 3 years (1995).

Estimated start and completion dates:

The study started in April 1990 and was completed July 1993.

Protocol number/title: HEPI 013 - Study on Advanced Breast Cancer.

Objective(s):

Multinational, randomized phase III open-label study comparing an intensive Epirubicin-containing regimen including Cyclophosphamide and 5-Fluorouracil with a conventional dose, non-anthracycline combination (CMF) in patients with metastatic breast cancer.

Design:

Multicentric, multinational, open label, randomised phase III trial.

Patient Population:

Patients with metastatic breast cancer, chemotherapy-naïve for this stage of disease.

Dosing plan / treatment plan / schema:

Arm A (FEC): 5-Fluorouracil 500 mg/m² iv d 1,8 q.3 weeks
Epirubicin 50 mg/m² iv d 1,8 q.3 weeks

Cyclophosphamide 400 mg/m² iv d 1,8 q.3weeks

Arm B (CMF): 5-Fluorouracil 600 mg/m² iv d 1,8 q.3 weeks
Methotrexate 40 mg/m² iv d 1,8 q.3 weeks
Cyclophosphamide 500 mg/m² iv d 1,8 q.3weeks

Efficacy Endpoints: Primary: TTP

Secondary: RR, Response duration, OS.

Definition of Endpoints:

TTP: From date of randomization to the first date of documented progression.

RR: WHO criteria (Miller et al.) except for overall response which was made on the basis of the lesion measurement irrespective of the organ site response.

Duration of response: From the date of first documented response to the first date of documented tumor progression.

OS: Time in days from the date of randomisation to the date of death or last follow-up.

Safety Monitoring:

Hematological assessment every week, non-hematological and clinical assessment every 3 weeks, cardiac evaluation (MUGA-scan or ECHO) at least every 2 cycles of FEC chemotherapy.

Statistical Plan:

Sample size/basis: 400 patients (200 each arm) to reject the null hypothesis of equal TTP at an alfa level 0.05 enabling a power of 0.80 for the alternative hypothesis.

Analyses: Stratification was made based on center, prior adjuvant chemotherapy, presence or absence of visceral metastases and number of organs involved by distant metastases (1-2 vs.>2).

Tests on primary and secondary endpoints: Time-related parameters were estimated by Kaplan-Meier and the two treatments were compared by log-rank and Wilcox tests. For TTP, a Cox proportional hazard regression analysis was performed.

Interim analysis plan: Not applicable.

Estimated start and completion dates: The study was completed. (Sept. 1990-Nov. 1992).

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information

**FEDERAL REGISTER
NOTICES; OTC or DESI
DOCUMENTS**

FEDERAL REGISTER
Vol. 64, No. 97

Notices

DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS)
Public Health Service (PHS)
Food and Drug Administration (FDA)

Oncologic Drugs Advisory Committee; Notice of Meeting

64 FR 27581

DATE: Thursday, May 20, 1999

ACTION: Notice.

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To view a specific page, transmit p* and the page number, e.g. p*1
----- [*27581]

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). At least one portion of the meeting will be closed to the public.

Name of Committee: Oncologic Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA's regulatory issues.

Date and Time: The meeting will be held on June 7 and 8, 1999, 8 a.m. to 5:30 p.m.

Location: Town Center Hotel, Maryland Ballroom, 8727 Colesville Rd., Silver Spring, MD.

Contact Person: Karen M. Templeton-Somers, Center for Drug Evaluation and Research (HFD-21), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20057, 301-827-7001, or FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area), code 12542. Please call the Information Line for up-to-date information on this meeting.

Agenda: The committee will discuss: (1) The use of time-to-progression as the primary endpoint in breast cancer drug trials; and (2) new drug application (NDA) 21-010, epirubicin hydrochloride for injection, Pharmacia and Upjohn Co., indicated for use as a component of adjuvant therapy in patients with evidence of axillary-node-tumor involvement following resection of primary breast cancer (Stage II & III). Epirubicin is indicated for the therapy of patients with locally advanced or metastatic breast cancer. On June 8, 1999, the committee will discuss: (1) NDA 50-718/S-006, Doxil (R) (doxorubicin HCl liposome injection), Alza Corp., indicated for the treatment of patients with metastatic carcinoma of the ovary who are refractory to both paclitaxel- and platinum-based chemotherapy regimens and who may also be refractory to topotecan. Refractory is defined as a patient having progressive disease while on treatment, or within 6 months of completing treatment; and (2) NDA 20-221/S-012, Etyol (R) (amifostine) for injection, U.S. Bioscience, Inc., indicated for use to reduce the incidence and severity of radiation induced xerostomia.

Procedure: On June 7, 1999, from 10:30 a.m. to 5:30 p.m., the meeting is open to the public. Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by May 28, 1999. Oral presentations from the public will be scheduled between approximately 10:45 [*27582] a.m. and 11 a.m. and 1:45 p.m. and 2:15 p.m. on June 7, 1999, and between approximately 8:15 a.m. and 8:45 a.m. on June 8, 1999. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before May 28, 1999, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed

participants, and an indication of the approximate time requested to make their presentation. After the scientific presentations, a 15-minute open public session will be conducted for interested persons who have submitted their request to speak by May 28, 1999, to address issues specific to the submission or topic before the committee.

Closed Committee Deliberations: On June 7, 1999, from 8 a.m. to 10 a.m., the meeting will be closed to permit discussion and review of trade secret and/or confidential information (5 U.S.C. 552b(c)(4)). This portion of the meeting will be closed to permit discussion of this information.

FDA regrets that it was unable to publish this notice 15 days prior to the June 7 and 8, 1999, Oncologic Drugs Advisory Committee meeting. Because the agency believes there is some urgency to bring these issues to public discussion and qualified members of the Oncologic Drugs Advisory Committee were available at this time, the Commissioner concluded that it was in the public interest to hold this meeting even if there was not sufficient time for the customary 15-day public notice.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: May 14, 1999.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 99-12852 Filed 5-18-99; 11:31 am]

BILLING CODE 4160-01-F

**ADVERTISING MATERIAL
REVIEW**

DOES NOT APPLY

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. LICANT'S NAME AND ADDRESS

Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

3. PRODUCT NAME

Epirubicin-Hydrochloride for Injection

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE
AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY
REFERENCE TO _____

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(616) 833-3825

5. USER FEE I.D. NUMBER

3623

6. LICENSE NUMBER / NDA NUMBER

NDA No. 21-010

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT
APPROVED UNDER SECTION 505 OF THE FEDERAL
FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN
EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,
Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT
QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of
the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL
GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED
COMMERCIALY
(Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR
TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT
FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT
LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL
APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not
required to respond to, a collection of information unless it
displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

DATE

Regulatory Manager

12/15/98

NDA # 31-010 DOCUMENT ID/LETTER DATE (N) 12-15-98
APPLICANT NAME Pharmacia & Upjohn
PRODUCT NAME Epirubicin hydrochloride for Injection

FORM MUST BE COMPLETED ASAP

1. YES User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM:

PLEASE MAKE THE FOLLOWING CHANGES TO THE COMIS DATA ELEMENTS

2. YES NO

CLINICAL DATA?

[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. "Clinical data do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?

3. YES NO

NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION	FEE	NO FEE
N _____	_____	FEE	NO FEE
N _____	_____	FEE	NO FEE

4. YES NO

BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT

[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N _____	_____	N _____	_____

5. P S

PRIORITY OR STANDARD?

6. CSO SIGNATURE/DATE

SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-5

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confidential

commercial

information

CENTER FOR DRUG EVALUATION AND RESEARCH
OGC TRACKING INFORMATION FORM

PART I - TO BE COMPLETED BY REQUESTING OFFICE/DIVISION

SUBJECT NAME: *ELLENCE (epirubicin hydrochloride)*

DATE SENT TO OGC: *6/14/99*

PROJECT DESCRIPTION (Name of document or brief description; include NDA/IND/ANDA Number, if applicable):

NDA 50-778 (formerly NDA 21-010)

Reclassification of epirubicin to an "old" antibiotic and exclusivity implications

DOCKET #/RES #/RIN (for Policy Staff Use Only):

OFFICE/DIVISION ORIGINATING REQUEST: *HFD-150*

TARGET DUE DATE (MO/DA/YR): *June 9, 1999 (NDA User Fee Date is June 15, 1999)*

PROGRAM CONTACT PERSON (Phone, Fax):

Patrick Guinn (301) 594-5767 FAX (301) 594-0499

REGULATORY POLICY STAFF CONTACT PERSON (Phone, Fax):

OGC Contact Person (if known):

PRIORITY (check one):

☒ **HIGH**

☐ **MEDIUM**

☐ **LOW**

TYPE OF PROJECT (check one):

☐ **FEDERAL REGISTER DOCUMENT** (check appropriate designation):

☐ **ADVANCED NOTICE OF PROPOSED RULE MAKING**

☐ **PROPOSED RULE**

☐ **FINAL RULE**

☐ **INTERIM RULE**

☐ **NOTICE OF MEETING**

☐ **FINAL ORDER**

☐ **DEBARMENT ORDER**

☐ **NOTICE OF OPPORTUNITY FOR HEARING**

☐ **ICH DOCUMENT** (CYCLE# ____; STEP# ____)

☐ **NOTICE OF HEARING**

☐ **CITIZEN'S PETITION**

☐ **ANDA SUITABILITY PETITION**

☒ **QUESTION/OPINION** (Any request for advice, review or concurrence other than petitions or Federal Register notices)

☐ **PROPOSED ENFORCEMENT ACTION**

☐ **OTHER:** _____ (e.g., guideline)

REQUESTED ACTION (check one):

☐ **CONCURRENT CLEARANCE** (review by OGC staff)

☐ **FINAL CLEARANCE** (review by A. Wion or M. Porter or designee)

☒ **PROVIDE COMMENTS**

☐ **REVIEW FOR MEETING** (MEETING TOPIC: _____; DATE: _____)

☐ **OTHER:** _____

OFFICE/DIVISION DIRECTOR'S SIGNATURE: _____

PLEASE SUBMIT A COPY OF ALL REQUESTS TO THE ASSOCIATE DIRECTOR FOR POLICY, HFD-5

PART II - TO BE COMPLETED BY OGC

DATE RECEIVED BY OGC:

DATE COMPLETED:

OGC CONTACT PERSON:

ACTION BY OGC:

☐ **DOCUMENT CLEARED**

☐ **DOCUMENT DENIED CLEARANCE**

☐ **COMMENTS PROVIDED**

☐ **OTHER:** _____

OGC SIGNATURE:



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
Denise S. Tindle
Regulatory Manager
Regulatory Affairs

Phone: 616/833-3825
Fax: 616/833-8237

DUPLICATE

NEW CORRESP
(NC)

June 1, 1999

Division of Oncology Drug Products HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
1451 Rockville Pike
Rockville, MD 20852



General Correspondence

RE: NDA 21-010 (NDA 50-778)
Epirubicin Hydrochloride Injection

Dear Sir/Madam:

Pharmacia and Upjohn would like to request a meeting with FDA during the week of June 1, 1999 regarding the classification of NDA 21-010/NDA 50-778 (epirubicin hydrochloride injection). Specific issues we would like to discuss are:

- FDA's classification of epirubicin hydrochloride injection as an "old antibiotic";
- Potential for delay in issuance of an action letter until the classification issue is resolved.

Our primary attendee will be Goran Ando M.D. Executive Vice President of Research and Development. Pharmacia & Upjohn also anticipates sending attendees from Clinical Development, Global Regulatory Affairs and Pharmaceutical Development.

We would like to request the attendance of Dr. Robert Temple and Dr. Jane Axelrad at this meeting.

Sincerely,

PHARMACIA & UPJOHN COMPANY
Denise S. Tindle
Regulatory Affairs Manager

cc: Mr. Patrick Guinn (FDA)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338

Expiration Date: April 30, 2000

See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

21-010 (50-778)

APPLICANT INFORMATION

NAME OF APPLICANT

Pharmacia & Upjohn Company

DATE OF SUBMISSION

June 1, 1999

TELEPHONE NO. (Include Area Code)

616-833-3825

FACSIMILE (FAX) Number (Include Area Code)

616-833-8237

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

7000 Portage Road
Kalamazoo, Michigan 49001

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Epirubicin Hydrochloride Injection

PROPRIETARY NAME (trade name) IF ANY

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

CODE NAME (If any)

DOSAGE FORM:

Preservative free solution

STRENGTHS: 10mg/5ml, 20mg/10ml,

50mg/25ml, 150mg/75ml, 200mg/100ml

ROUTE OF ADMINISTRATION:

Intravenous

(PROPOSED) INDICATION(S) FOR USE: Breast Cancer

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

☒ NEW DRUG APPLICATION (21 CFR 314.50)☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

☒ 505 (b) (1)☐ 505 (b) (2)☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Holder of Approved Application

TYPE OF SUBMISSION

(check one)

☐ ORIGINAL APPLICATION☐ AMENDMENT TO A PENDING APPLICATION☐ RESUBMISSION☐ PRESUBMISSION☐ ANNUAL REPORT☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT☐ SUPAC SUPPLEMENT☐ EFFICACY SUPPLEMENT☐ LABELING SUPPLEMENT☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT☒ OTHER

REASON FOR SUBMISSION

General Correspondence - Requesting Meeting

PROPOSED MARKETING STATUS (check one)

☒ PRESCRIPTION PRODUCT (Rx)☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

☒ PAPER☐ PAPER AND ELECTRONIC☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Pharmacia & Upjohn (Perth) Pty. Limited [drug product]
Bentley WA 6102 AustraliaFurther details regarding Establishment Information is provided
in Attachment 5 of NDA submission.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

ND

EF

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pages of trade

secret and/or

confidential

commercial (b)(5)

information

Pharmacia & Upjohn

Regulatory Affairs

To: Mr. Patrick Guinn

Fax No: (301) 594-0499

Subject: NDA 21-010 (NDA 50-778), Epirubicin Hydrochloride Injection

From: Denise Tindle

Tel No: (616) 833-3825

Fax No: 616-833-0409

Date: June 2, 1999

Pages (including this one): 8

Epirubicin hydrochloride injection-NDA 21-010 (NDA 50-778)

Dear Patrick,

Please see the attached letter presenting Pharmacia & Upjohn's position with regard to FDA's classification of epirubicin hydrochloride injection.

Sincerely,



Denise Tindle
Regulatory Manager
Pharmacia & Upjohn

PHARMACIA & UPJOHN, 7000 Portage Road, Kalamazoo, MI 49001

Confidentiality Note: The documents accompanying this telecopy transmission contain information belonging to Pharmacia & Upjohn, which is intended only for the use of the addressee. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this telecopied information is strictly prohibited. If you have received this telecopy in error, please immediately notify us by telephone to arrange for the return of the original documents to us. Thank you.

**Pharmacia & Upjohn**7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000Office of:
Denise S. Tindle
Regulatory Manager
Regulatory AffairsPhone: 616/833-3825
Fax: 616/833-8237

June 2, 1999

Division of Oncology Drug Products HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852**RE: NDA 21-010 (NDA 50-778)
Epirubicin Hydrochloride Injection****General Correspondence**

Dear Dr. Justice,

This letter will serve to present Pharmacia & Upjohn's (P&U) position with regard to FDA's recent determination that NDA 21-010 (epirubicin hydrochloride injection) is "for an antibiotic" within the meaning of the Federal Food Drug and Cosmetic Act (Act) and therefore exempt from the patent listing, patent certification, and exclusivity provisions of section 505 of the Act. For the reasons set forth more fully below, P&U strongly disagrees with FDA's decision to reclassify this drug, especially at this late stage in the review cycle of the application.

I. Factual Background

A NDA for marketing approval of epirubicin for the treatment of advanced breast cancer (second-line therapy) was filed in 1984 by Adria Laboratories and found not approvable by FDA in 1986. P&U, having the rights to this drug, is currently seeking approval as adjunctive therapy in early breast cancer and as first-line therapy in metastatic breast cancer. This completely new NDA, which was filed in December 1998, was granted a priority therapeutic classification by FDA and P&U is anticipating its review by the Oncology Drugs Advisory Committee (ODAC) on June 7, 1999. However, on May 21, 1999, P&U was informed by FDA that because of the previous epirubicin application, the Agency is considering the drug to be an "old" antibiotic. As such, epirubicin would not be eligible for non-patent market exclusivity pursuant to the Hatch-Waxman provisions of Act. Below are some relevant milestones in the regulatory history of epirubicin:

NDA 21-010

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- On July 13, 1984, Adria Laboratories informed FDA that it would be submitting a NDA for epirubicin hydrochloride, and that NDA — had been preassigned by FDA.
- NDA — epirubicin HCl for Injection, was submitted to FDA by Adria Laboratories on July 23, 1984, and stamped "Received" by FDA on July 24, 1984.
- A July 25, 1984 Adria Laboratories internal memorandum of a telephone conversation with FDA indicates that FDA informed Adria Laboratories that it had assigned epirubicin an incorrect NDA number and would reassign it a number in the 50,000 series (—) since, in the FDA's view, the product was an antibiotic.
- A September 10, 1984 letter from FDA to Adria Laboratories acknowledges receipt of the NDA pursuant to section 505(b) of the Act (the new drug application provision), and lists July 17, 1984 as the date of receipt.
- A July 10, 1985 letter to Adria Laboratories from FDA, regarding NDA — , states that the NDA "dated July 13, 1984 submitted pursuant to section 502(b)^{1/}" "is not approvable under section 507 of the Act," (the antibiotic drug section). The primary reason was the lack of single-agent studies.
- A July 19, 1985 letter to FDA from Adria Laboratories clarifies that the NDA was "filed pursuant to 505(b) rather than 502(b)" and Adria Laboratories intends to amend the NDA. FDA did not respond to this clarification.
- On April 9, 1998, a Pre-NDA Guidance Meeting with FDA was held during which FDA indicated that an epirubicin NDA would likely receive priority review.
- On November 20, 1998, FDA issued an acknowledgment letter to P&U for the pre-submission of Preclinical and Pharmacokinetics/Bioavailability information for epirubicin which cites an FDA Reference Number of NDA 21-010.
- During a teleconference on January 29, 1999, FDA acknowledged that NDA 21-010 was fileable and would receive a priority review with a User Fee Date of June 15, 1999.
- On February 2, 1999, FDA issued a letter to P&U indicating receipt of the NDA on December 15, 1998 under section 505(b) of the Act. As of the date of this letter, the NDA had in fact already been filed.
- On May 21, 1999, P&U received a fax from FDA (Patrick Guinn, Project Manager) which stated that: "Upon determining that your application NDA 21-010 is for an antibiotic," and that the NDA reference number had been changed to 50-778. The fax also states that the application is considered a submission of an "old" antibiotic because a NDA for epirubicin was submitted prior to November 20, 1997.

^{1/} This appears to be a typographical error, as 502(b) is the misbranding section of the Act; section 505(b) is the new drug approval section.

NDA 21-010

Page 3

In sum, the original epirubicin application was submitted by Adria Laboratories and received by FDA as a NDA under section 505(b) for an oncology indication more than 13 years prior to the passage of the Food and Drug Administration Modernization Act of 1997 (FDAMA). FDA subsequently converted it to an antibiotic application. The application was deemed not approvable and was never amended. A completely new NDA for epirubicin was submitted by P&U more than a year after the passage of FDAMA which was received and filed by FDA under 505(b) and granted priority review because the drug would be a significant improvement over other therapies for the adjuvant treatment of breast cancer.

II. Legal and Regulatory Framework

A. "Old Antibiotics"

Prior to the enactment of FDAMA, antibiotics were approved under section 507 of the Act. Since Hatch-Waxman non-patent exclusivity only applied to drugs approved under section 505, antibiotics were not then eligible for such exclusivity.

Section 125 of FDAMA eliminated section 507 entirely, such that antibiotics are now reviewed and approved under section 505, no differently than any other drugs,^{2/} and are now also eligible for exclusivity. In so doing, Congress recognized that market exclusivity would provide an appropriate incentive for the development of new antibiotics. However, the transition provision located in section 125(d)(2) of FDAMA states that section 505 of the Act:

shall not apply to any application for marketing in which the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing *received by the Secretary of Health and Human services under section 507* [emphasis added] of such Act . . .

Thus, an "old antibiotic," i.e., an antibiotic that was the subject of an application filed under section 507 prior to FDAMA, is not eligible for Hatch-Waxman exclusivity.^{3/} FDA's Guidance document

^{2/} As stated in Reinventing Regulation of Drugs and Medical Devices, (National Performance Review, 1995): "[w]hen Congress enacted those sections of the Federal Food, Drug, and Cosmetic Act, detailed regulations setting forth standards and tests were thought to be necessary to ensure the quality and the safety of these products. At the time, Congress also expressly recognized, at least with respect to antibiotics, that a time would come when manufacturing technology would overcome the need for such detailed regulation and that the manufacturing controls used for chemically synthesized drugs would suffice for antibiotics as well."

^{3/} The House report states: "The Committee intends that the granting of market exclusivity be limited to products that achieve the policy objective of increasing research toward the development of new antibiotics. Thus, the granting of market exclusivity to new antibiotic drugs is limited to those products that are New Chemical Entities and to products for which a New Drug Application has not been submitted prior to enactment." H. Rep. 105-310, Prescription Drug User Fee Reauthorization and Drug Regulatory Modernization Act of 1997, at 77.

NDA 21-010

Page 4

regarding the repeal of Section 507 provides further examples of which applications the Agency considers to have been received prior to FDAMA, including any antibiotic application:

- Received by FDA (as evidenced by an Agency date stamp) on or before November 20, 1997;
- filed or approved on or before November 20, 1997;
- the subject of an action letter on or before November 20, 1997;
- received on or before November 20, 1997, withdrawn and not further submitted.^{4/}

FDA's Antibiotic Regulation Repeal Working Group is reportedly compiling a list of "old antibiotics," but this list has not yet issued. Thus, there is no clear indication from FDA as to which drugs are considered to be old antibiotics.

B. Definition of Antibiotic

The definition of an antibiotic drug did not change with FDAMA. New section 201(jj) of the Act defines an antibiotic drug as:

any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for use by man containing any quantity of any chemical substance which is produced by a micro-organism *and* which has the capacity to inhibit or destroy micro-organisms *in dilute solution* [all emphases added] (including the chemically synthesized equivalent of any such substance) or any derivative thereof.

This broad definition focuses on whether the drug is produced by micro-organisms, and could be used to destroy micro-organisms, but does not overtly address the intended use of the drug. FDA's regulations set forth a list of antibiotic substances at 21 C.F.R. § 430.4. This list does not specifically include "epirubicin" or "epirubicin hydrochloride".

III. Rebuttal to FDA's Interpretation

P&U disputes FDA's characterization of epirubicin as an "old antibiotic" on both factual and policy grounds. Support for this position is set forth below:

A. Factual Grounds

- Epirubicin is not an Antibiotic: Epirubicin should not be regulated as an antibiotic because it does not meet the statutory definition. As defined in the Act, an antibiotic is a chemical substance which is produced by a microorganism and which has the capacity to inhibit or

^{4/} This list is not exhaustive. See, Guidance for Industry and Reviewers; Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act (May 1998).

NDA 21-010

Page 5

destroy microorganisms in dilute solution. Epirubicin is a semisynthetic derivative of a drug that is produced by microorganisms. However, the drug has been exclusively developed for its cytotoxic mechanism of action against eukaryotic cells and not as an antimicrobial agent. Relevant dilution of an antibiotic is considered most readily achieved by in vivo administration. P&U has no data or information which indicates that epirubicin would have antimicrobial activity or any pharmacologically useful properties as an antibiotic in this setting. Since the FDA has not provided to P&U any information which would support its apparent conclusion that epirubicin does possess antimicrobial activity in dilute solution, it would be inappropriate to classify it as an antibiotic.

- The original NDA was not received under Section 507: Epirubicin should not be considered an "old antibiotic" because it was not the subject of an application "received by the Secretary . . . under section 507." The original epirubicin NDA was filed by Adria Laboratories as a drug application under section 505, as evidenced by the pre-assigned NDA number. Further, prior to FDA's unilateral conversion of it to an antibiotic application, the submission was stamped "received" by FDA's Bureau of Drugs. Finally, FDA's September 10, 1984 letter of receipt of the NDA clearly indicates that it was received under 505(b), and refers to a receipt date of July 17, 1984. Therefore, the plain and unambiguous language of FDAMA precludes FDA from reclassifying epirubicin as an "old" antibiotic.
- Disparate Treatment: Epirubicin should not be treated differently from other, more recently approved cytotoxic drugs. Nipent (pentostatin for injection) and Novantrone (mitoxantrone for injection concentrate), for example, are listed as antineoplastic antibiotics in the Physicians Desk Reference, yet appear to have been regulated as non-antibiotic drugs by FDA.^{5/} Under well established principles of administrative law, the failure of FDA to treat epirubicin in the same fashion as these more recently approved cytotoxic agents or to provide a rational basis for such disparate treatment could be viewed as arbitrary and capricious Agency action in violation of the Administrative Procedure Act.^{6/}

B. Equitable Concerns

- Development Incentive: With the enactment of FDAMA in 1997, Congress repealed section 507 so that antibiotics would be treated in the same manner as other drugs under the Act. As a result of this change, additional incentives to develop new antibiotics were created. In limiting exclusivity to those antibiotics for which applications had not yet been submitted, Congress aimed to prevent the awarding of exclusivity to those companies that had already completed product development. This limitation should not apply to P&U because development was not complete prior to FDAMA and the incentive was necessary.

While a NDA for epirubicin was filed for use as second-line therapy in advanced breast cancer in 1984, the FDA did not approve it for that indication. Subsequent to the passage of FDAMA, P&U substantially developed, collected, analyzed, collated and documented data

^{5/} Nipent's NDA number is 20-122 and Novantrone's is 19-297. Novantrone has patent and exclusivity data listed in the Orange Book and while Nipent has no listings in the current Orange Book, it did have exclusivity listed earlier which expired on October 11, 1998.

^{6/} See Bracco Diagnostics v. Shalala, 963 F. Supp. 20 (D.D.C. 1997).

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and information relevant to epirubicin's intended use as an antineoplastic agent that can prolong survival when given as adjuvant therapy to women with early breast cancer. P&U has similarly developed information that would support therapy for first-line use in metastatic breast cancer. In addition, P&U has conducted pharmaceutical development to enhance the stability and the ease and safety of preparation and administration of the pharmaceutical formulation. This level of activity underscores P&U's commitment to fully develop this chemotherapeutic agent. P&U's active efforts to fully develop the drug have taken place in the last few years and have focused on adjuvant and first-line therapy. Therefore, awarding the incentive is consistent with the spirit and intent of FDAMA.

- **Detrimental Reliance:** P&U has pursued this NDA with the good faith expectation that exclusivity would apply. Clearly a 20,000 series NDA number, rather than an antibiotic series number, was assigned to this NDA despite the fact that it was filed after issuance of FDA's Guidance on the repeal of section 507. Indeed, this Guidance document specifically states that "Series 20,000 numbers will be assigned to all marketing applications submitted under 505(b) on or after November 21, 1997, *to which the section 125 exemptions do not apply* [emphasis added]." It is only quite recently, a mere two weeks from ODAC review of the drug, that FDA communicated with P&U regarding the apparent switch to an antibiotic classification. P&U substantially relied upon the receipt and filing of the new epirubicin NDA as a non-antibiotic drug, a logical and understandable conclusion given its further development and intended use as a cancer treatment. P&U could not have been expected to pursue the approval thus far without the expectation of market exclusivity. It is therefore fundamentally unreasonable and inequitable and would serve no apparent public health interest for FDA to essentially change the rules - or its interpretation of the rules in this case - at the eleventh hour.
- **Public Health Need:** Based on the survival advantage offered by epirubicin to women suffering from early breast cancer, we believe that this drug would be an important addition to existing oncology treatment options. As indicated by FDA's Dr. Susan Honig in her review of the epirubicin NDA (Medical Officer Review of NDA 21-010, Section 3.2.4, page 12; May 26, 1999): "There are no cytotoxic agents specifically labeled for adjuvant breast cancer treatment." As additionally indicated by Dr. Honig: "No cytotoxic agents have a specific indication for first-line therapy of metastatic breast cancer." Her concluding remarks in this section of her review were: "If approved, epirubicin will be the first drug to obtain these specific indications for breast cancer treatment." These data collectively indicate that epirubicin is viewed by FDA as a cytotoxic drug that will likely be approved for uniquely new indications. For these reasons, we do not wish to be placed in a position where we would be unable to make this product available to the American public or to continue to support its clinical development. It is within FDA's power through appropriate classification to grant exclusivity to epirubicin and provide an avenue for this to happen.

IV. Summary and Conclusions

In sum, epirubicin should not be regulated as an "old antibiotic" because it was not received under section 507 of the Act prior to 1997, it does not meet the statutory definition of an antibiotic, and because FDA has regulated other oncology drugs, which have certain antibiotic characteristics, as non-antibiotic drugs. Moreover, the legislative intent of section 125(d)(2) of FDAMA was clearly to prevent applicants from simply withdrawing their pending antibiotic (section 507) applications immediately prior to passage of FDAMA and subsequently refiled them, thereby obtaining

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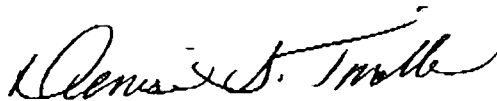
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exclusivity when such would not have otherwise been warranted. As FDA is well aware, this was clearly not the situation with epirubicin. Finally, fundamental principles of fairness and equity demand that P&U's reliance on FDA's receipt and filing of NDA 21-010, after issuance of its guidance document, should not accrue to its detriment. Pharmacia & Upjohn wishes to resolve this matter expeditiously and will attempt to obtain a meeting with the appropriate members of CDER management. In the interim, we hereby request that no formal approval decision be made by FDA with respect to epirubicin until this matter is resolved.

If you have any questions related to this submission, please contact me at (616) 833-3825 or address correspondence to mailstop 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Denise S. Tindle
Regulatory Affairs Manager

DST:lmf
Attachments

cc: Dr. Jane Axelrad (FDA)
cc: Mr. Patrick Guinn (FDA)
cc: Dr. Robert Justice (FDA)
cc: Dr. Max Lumpkin (FDA)
cc: Dr. Robert Temple (FDA)